REMARKS

Claims 1-2, 4-8 and 12-14 and16 are currently pending. Claims 4 and 15 have been amended for clarity. A "clean" claim set to be introduced in place of the original claims is provided above and a version showing changes made and an appendix of pending claims is attached for the Examiner's convenience.

Rejections under 35 U.S.C § 112, second paragraph

Claims 4-7 and 15 were rejected under 35 U.S.C § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner states that the term "the percentage" lacks antecedent basis and it is unclear what is encompassed by "all of part of a sequence". Although Applicants believe that one with ordinary skill in the art would be able to understand the meaning of the terms as claimed, Applicants have amended claims 4 and 15 for clarity. Support for the amendment can be found throughout the specification. See specification at page 6, lines 21-23; page 7, lines 1-5 and page 7, lines 12-16 (defining neural progenitor cell and specifying the use of RET as an antigen to generate antibodies that bind to at least part of the sequence used to generate the antibodies).

Rejections under 35 U.S.C. § 102(b)

Claims 8 and 16, and claims 13-14 as dependent from claim 16, were rejected under 35 U.S.C. § 102(b) as being anticipated by Stemple et al. (Cell 71: 973-985, 1992).

Stemple et al. is directed toward the isolation of mammalian neural crest cells using a monoclonal antibody to the low affinity NGF receptor and the establishment of conditions for the serial propagation of these cells in clonal culture to assess their developmental potential.

Stemple et al. does not teach the use of an antibody to the RET protein. In addition Stemple et al. does not teach a substantially pure population of neural crest derived neural progenitor cells comprising RET protein. Stemple et al uses only antibodies to the NGF receptor. Applicants point out in the specification that anti-RET and Anti-LNGFR antibodies enrich for distinct populations of neural crest derived cells. See specification at page 26, lines 6-27.

Therefore Stemple et al. does not disclose claim 16, a substantially pure population of neural crest derived neural progenitor cells comprising RET protein prepared using antibody binding to RET protein, where said cells are proneuronal progenitor (proNP) cells, neuronal progenitor (NP) cells and/or nonneuronal progenitor (NNP) cells.

The law is well established that in order to anticipate a claim, the prior art must disclose "each and every element"of the claimed invention. SSIH Equipment S.A.v. U.S. Inc. Int'l. Trade Commission, 218 USPQ 678, 688 (Fed. Cir. 1983). As stated by the Federal Circuit in In re Bond, 15 USPQ2d 1566, 1567 (Fed. Cir. 1990), "[f]or a prior art reference to anticipate in terms of 35 U.S.C. § 102, every element of the claimed invention must be identically shown in a single reference." (Emphasis added). See also Glaverbel Societe Anonyme v. Northlake Marketing & Supply, Inc., 33 USPQ2d 1496 (Fed. Cir. 1995).

Any degree of physical difference between the patented product and the prior art, no matter how slight, defeats the claim of anticipation, Chisum volume 1 § 3.02 citing to, *Transco*

Products Inc. v. Performance Contracting, Inc., 792 F. Supp. 594, 23 USPQ2d 1691 (N.D. III. 1992).

The prior art does not disclose "each and every element" of the claimed invention. Accordingly, the reference does not anticipate the present claims, and the rejection is improper.

Rejections under 35 U.S.C. § 103 (a)

Claims 1, 2, 4-8, and 12-16 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Lo et al. (Perspectives Dev. Neurobiol. 2: 191-201, 1994), Stemple et al. (Dev. Biol. 159: 12-23, 1993), Stemple et al. (Cell 71: 973-985, 1992), and Martucciello et al.

Lo et al. is directed to the expression patterns of markers such as Mash-1 and c-RET in neural crest development. Lo et al. also looked at expression of differentiation markers within the null mutation of Mash-1 as compared to wild type embryos. In situ hybridization experiments were performed using RNA probes directed to various differentiation markers using different tissue sections and different stages of development. Lo et al. does not teach the enrichment of neural progenitor cells having an 8-9 times enrichment of neuronal progenitor cells that generate progeny that differentiate into neurons after only a few divisions. This is an unexpected result not taught in any of the cited prior art references. See specification at page 32, lines 10-25.

Stemple et al. (Dev. Biol. 159: 12-23, 1993) is directed to a review of various environmental factors affecting growth and differentiation of neural crest development Although Stemple et al. discusses the use of antibodies to cell surface antigens as a means of purifying subpopulations of cells within a mixture, it does not mention the RET protein at all.

Stemple et al. (Cell 71: 973-985, 1992) is directed to the isolation of stem cells for neurons and glia from the neural crest using antibodies against the low affinity NGF receptor. Stemple et al. does not mention the RET protein at all.

Martucciello et al. is directed to the immunohistochemical study of expression and localization of the RET protein in the intestinal plexuses of patients with Hirschsprung's disease. Immunohistochemistry was performed with monoclonal and polyclonal antibodies against the RET protein. Martucciello et al. does not teach for the enrichment of individual cell lineages from neural crest stem cells that are RET^+. Martucciello et al. only looks at tissues, not at individual cells for the expression pattern of the RET protein.

The Examiner appears to state that it would have been obvious to combine the antibodies used in Martucciello et al. with the methods of isolating cells taught in Stemple et al. (Cell 71: 973-985, 1992) to arrive at the composition of cells in the claims of the present invention.

To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). The mere fact that references can be combined or modified does not render the resultant combination obvious

unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F 2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990).

That features, even distinguishing features, of the claimed invention are disclosed in the prior art is not alone sufficient to compel a conclusion of obviousness. It is common to find features somewhere in the prior art, but it is not features but the subject matter as a whole that must be evaluated under 35 U.S.C § 103. *In re Dillon*, 919 F. 2d 688, Fed Cir. 1990.

To be patentable, a compound need not excel over prior art compounds in all common properties. Evidence that a compound is unexpectedly superior in one of a spectrum of common properties can be enough to rebut a prima facie case of obviousness. *In re Chupp*, 816 F2d 643, 2 USPQ 2d 1437 (Fed. Cir. 1987).

First the composition claims of the present invention are novel as the prior art does not teach or suggest the lineages of the current claims. The cell lineages are distinct from lineages taught in the prior art. The proNPs of the present invention generate progeny that differentiate to neurons only after a few divisions as opposed to neural crest stem cells of the prior art, which appear to undergo at least 6-10 rounds of symmetric, self-renewing division before emergence of distinct neuronal and glial lineages. See specification at page 32, lines 7-12. Further proNPs are insensitive to environmental influences such as GGF and fibronectin whereas the clones of neural crest stem cells exhibit a delay or repression of neuronal differentiation upon exposure to these environmental factors.

Although methods for isolating cells based on various antigenic markers may be taught in the prior art, the claims of the present invention are for compositions of lineages of cells that are not taught in the prior art. The composition of neural progenitor cells isolated by using antibodies

to the RET protein was found to be more highly enriched in neuronal progenitors than cells isolated using antibodies to the low affinity NGF receptor. Neural progenitors which include neural crest stem cells are not equivalent to neuronal progenitor cells which give rise to neurons as opposed to glia cells, an enrichment that is not suggested or expected in any of the prior art references. See specification at page 32, lines 17-25.

None of the prior art references alone or in combination teach or suggest the particular composition of cells of the claims of the present invention. It is these specific compositions that distinguish the claims from the prior art. Specifically none of the prior art references teach or suggest claim 1 (A composition comprising a monoclonal antibody and a cell selected from the group consisting of a multipotent neuronal progenitor (proNP) cell, a nonneuronal progenitor (NNP) cell and a committed neuronal progenitor (NP) cell, each of which comprise RET protein, wherein said monoclonal antibody is specifically bound to all or part of a sequence of said RET protein on said cell) or claim 16 (A substantially pure population of neural crest derived neural progenitor cells comprising RET protein prepared using antibody binding to RET protein, where said cells are proneuronal progenitor (proNP) cells, neuronal progenitor (NP) cells and/or nonneuronal progenitor (NNP) cells), the only independent claims pending in the present application.

Accordingly, none of the cited prior art references teach or suggest all the claim limitaions and therefore the rejection is improper.

Applicants, therefore, respectfully request withdrawal of the rejections. Applicants respectfully submit that the claims are now in condition for allowance and early notification to that effect is respectfully requested. If the Examiner feels there are further unresolved issues, the

Examiner is respectfully requested to phone the undersigned at (415) 781-1989.

Respectfully submitted,

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